

### Amendments to the Specifications

Please replace paragraph 0101 with the following paragraph:

#### EXAMPLE 3

##### *Particle Size, Particle Density, and Rate of Inhalable Particle Formation of Metoprolol Aerosol*

[0101] A solution of 16.0 mg metoprolol in 100  $\mu\text{L}$  dichloromethane was spread out in a thin layer on the central portion of a 3.5 cm x 7 cm sheet of aluminum foil. The dichloromethane was allowed to evaporate. Assuming a drug density of about 1 g/cc, the calculated thickness of the metoprolol thin layer on the 24.5 cm<sup>2</sup> aluminum solid support, after solvent evaporation, is about 6.5 microns. The aluminum foil was wrapped around a 300 watt halogen tube, which was inserted into a T-shaped glass tube. Both of the openings of the tube were sealed with parafilm, which was punctured with fifteen needles for air flow. The third opening was connected to a 1 liter, 3-neck glass flask. The glass flask was further connected to a large piston capable of drawing 1.1 liters of air through the flask. Alternating current was run through the halogen bulb by application of 90 V using a variac connected to 110 V line power. Within 1 s, an aerosol appeared and was drawn into the 1 L flask by use of the piston, with collection of the aerosol terminated after 6 s. The aerosol was analyzed by connecting the 1 L flask to an eight-stage Andersen non-viable cascade impactor. Results are shown in table 1. MMAD of the collected aerosol was 1.4 microns with a geometric standard deviation of 2.0. Also shown in table 1 is the number of particles collected on the various stages of the cascade impactor, given by the mass collected on the stage divided by the mass of a typical particle trapped on that stage. The mass of a single particle of diameter D is given by the volume of the particle,  $\pi D^3/6$ , multiplied by the density of the drug (taken to be 1 g/cm<sup>3</sup>). The inhalable aerosol particle density is the sum of the numbers of particles collected on impactor stages 3 to 8 divided by the collection volume of 1 L, giving an inhalable aerosol particle density of  $8.6 \times 10^7$  particles/mL. The rate of inhalable aerosol particle formation is the sum of the numbers of particles collected on impactor stages 3 through 8 divided by the formation time of 6 s, giving a rate of inhalable aerosol particle formation of  $1.4 \times 10^{10}$  particles/second.

Please replace paragraph 0103 with the following paragraph:

**EXAMPLE 4**

*Drug Mass Density and Rate of Drug Aerosol Formation  
of Metoprolol Aerosol*

[0103] A solution of 12.7 mg metoprolol in 100  $\mu$ L dichloromethane was spread out in a thin layer on the central portion of a 3.5 cm x 7 cm sheet of aluminum foil. The dichloromethane was allowed to evaporate. Assuming a drug density of about 1g/cc, the calculated thickness of the metoprolol thin layer on the 24.5 cm<sup>2</sup> aluminum solid support, after solvent evaporation, is about 5.2 microns. The aluminum foil was wrapped around a 300 watt halogen tube, which was inserted into a T-shaped glass tube. Both of the openings of the tube were sealed with parafilm, which was punctured with fifteen needles for air flow. The third opening was connected to a 1 liter, 3-neck glass flask. The glass flask was further connected to a large piston capable of drawing 1.1 liters of air through the flask. Alternating current was run through the halogen bulb by application of 90 V using a variac connected to 110 V line power. Within seconds, an aerosol appeared and was drawn into the 1 L flask by use of the piston, with formation of the aerosol terminated after 6 s. The aerosol was allowed to sediment onto the walls of the 1 L flask for approximately 30 minutes. The flask was then extracted with acetonitrile and the extract analyzed by HPLC with detection by light absorption at 225 nm. Comparison with standards containing known amounts of metoprolol revealed that 6.4 mg of > 99% pure metoprolol had been collected in the flask, resulting in an aerosol drug mass density of 6.4 mg/L. The aluminum foil upon which the metoprolol had previously been coated was weighed following the experiment. Of the 12.7 mg originally coated on the aluminum, all of the material was found to have aerosolized in the 6 s time period, implying a rate of drug aerosol formation of 2.1 mg/s.